TERTIARY ALCOHOL DERIVATIVES OF 2-ACETYL THIOPHENE

A THESIS

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Master of Science in Chemistry

by

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TERTIARY ALCOHOL DERIVATIVES

OF 2-ACETYL THIOPHENE

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ACKNOWLEDGMENTS

On completion of this work I wish to express my sincere appreciation to Dr. E. Emmett Reid, not only for suggesting the problem, but also for his aid and guidance during its prosecution. I should also like to thank Dr. B. B. Wroth for his cooperation in this study.

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PURPOSE OF THIS INVESTIGATION

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CHAPTER I

PURPOSE OF THIS INVESTIGATION

In recent years comparatively large quantities of thiophene have been produced as a by product in the manufacture of butadiene and other processes. Its acylated derivative, 2-acetyl thiophene, has also become available (courtesy of Socony-Vacuum Company) and a study of some of the reactions of this compound was suggested.

The purpose of this investigation was to prepare a series of dialkyl substituted tertiary alcohols by the condensation of 2-acetyl thiophene with the lower alkyl magnesium halides through the Grignard reaction and make a study of their properties.

It has been found in the search for compounds having antihistaminic activity that certain pyridyl substituted alkamine ethers have a marked effect.[1] The synthesis of these ethers involves condensation of appropriately substituted carbinols with dialkyl amino alkyl halides and sodium amide in toluene.

The carbinols reported in this thesis are similar in structure to many of those used in the synthesis of these antihistaminic agents and therefore may find use in this field.

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[1] N. Sperber, D. Papa, E. Schwenk, and M. Sherlock, J. Am. Chem. Soc., 71, 887 (1949).

CHAPTER II

THE GRIGNARD REACTION WITH 2-ACETYL THIOPHENE

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THE GRIGNARD REACTION WITH 2-ACETYL THIOPHENE

The preparation of tertiary alcohols by reaction of an organo magnesium halide is well known in organic chemistry. This reaction to produce dialkyl substituted thienyl carbinols was first studied by Thomas[2] who prepared dimethyl 2-thienyl carbinol by the action of thienyl magnesium iodide on acetone. He also attempted to prepare methyl ethyl 2-thienyl carbinol and methyl amyl 2-thienyl carbinol by the action of methyl ethyl ketone and methyl amyl ketone respectively but was unable to obtain a pure product due to apparent dehydration of the alcohol and the difficulty in separating the alcohol-olefin mixture.

In this investigation the alkyl halides were reacted with 2-acetyl thiophene due to its ready availability as a starting material. Care was taken to work at the lowest temperatures possible and with extremely pure products in order to avoid the dehydration troubles encountered by the previous workers.

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[2]V. Thomas, Compte rend., 146, 643.

CHAPTER III

EXPERIMENTAL

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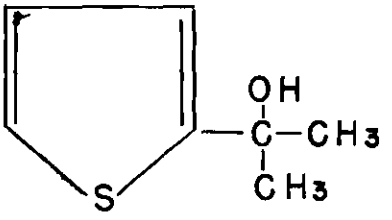
EXPERIMENTAL

Anhydrous Ether

The anhydrous ether used in this investigation was prepared by washing U.S.P. grade ether with brine solution and allowing it to stand over calcium chloride for several days. It was then filtered and dried over sodium wire until the reaction ceased and the wire remained bright. The ether was again filtered and distilled from phosphorous pentoxide.

Preparation of Dimethyl 2-Thienyl Carbinol I



The Grignard reagent, methyl magnesium iodide, was prepared by placing 18.2 grams (0.76 mole) of magnesium turnings in a 500 ml., three-necked flask which had been previously dried for several hours at 100 degrees C. The flask was equipped with a reflux condenser with a calcium chloride drying tube, a mechanical stirrer of the Hershberg type, and a dropping funnel. The flask was then heated with the direct flame of a bunsen burner to drive out all possible remaining moisture.

The system was then cooled and 108 grams (0.76 mole) of methyl iodide dissolved in 100 ml. absolute ether was dropped in very slowly over a period of thirty minutes. Cooling with ice was necessary to control the reaction and prevent excessive loss of the ether. The mixture was stirred fifteen minutes after the addition of the methyl iodide was complete.

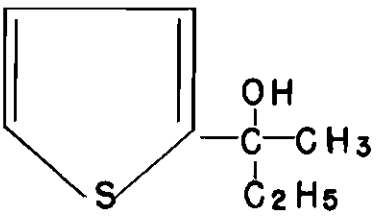
The Grignard solution was cooled to room temperature and fifty-seven grams (0.45 mole) of redistilled 2-acetyl thiophene was dropped in slowly over a period of thirty minutes. A heavy white precipitate formed in the flask and the mixture was stirred one hour after the addition of all the 2-acetyl thiophene.

The Grignard complex was hydrolyzed by slowly pouring over 300 grams of ice and water containing 15 ml. of concentrated sulfuric acid. This solution was filtered using a sintered glass filter to remove any unreacted magnesium. The filtrate was extracted five times with 100 ml. portions of ether. The ether extracts were combined and allowed to stand overnight over anhydrous potassium carbonate.

The ether was distilled off at 50 to 70 degrees C. using a water bath and the residue remaining was transferred to a 125 ml. distilling flask and distilled under reduced pressure. The pure product boiled at 104 degrees C. at 25 mm. pressure.

The carbinol was a colorless oil which solidified upon cooling to colorless prisms which melted at 30 degrees C. The yield was 21.5 grams or 33.2% of theoretical. The refractive index was found to be 1.5280 at 30 degrees C.

Preparation of Methyl Ethyl 2-Thienyl Carbinol II



Twelve grams (0.5 mole) of magnesium turnings were placed in a dry 500 ml. three-necked flask equipped with a reflux condenser with drying tube, mechanical stirrer, and dropping funnel. The system was heated to drive out moisture.

The flask was cooled and seventy-seven grams (0.5 mole) of ethyl iodide dissolved in 100 ml. of absolute ether was slowly dropped in over a period of thirty-five minutes. Cooling was necessary to control the reaction. The mixture was stirred fifteen minutes after all the ethyl iodide had been added.

The contents of the flask was cooled to room temperature and twenty-seven grams (0.215 mole) of 2-acetyl thiophene dissolved in 50 ml. of absolute ether was dropped in over a period of fifteen minutes. A heavy white precipitate formed in the flask and the mixture was stirred one hour after the addition of the 2-acetyl thiophene was complete.

The mass in the flask was filtered and the ether distilled off on a water bath at 50 to 70 degrees C. The residue was transferred to a 125 ml. distilling flask and distilled under reduced pressure. At 19 mm. the product had a boiling range of 85 to 100 degrees C. and

showed some signs of decomposition. A test for unsaturation (bromine in carbon tetrachloride) was applied and the product was found to be highly unsaturated. It was assumed that the alcohol had dehydrated and the product was a mixture of the alcohol and olefin. The per cent carbon and hydrogen found experimentally was 65.3% carbon and 7.43% hydrogen as compared with the calculated values of 61.5% and 7.70% for the carbinol and 69.6% and 7.25% for the olefin.

The preparation of the carbinol was repeated in the same manner, this time using eighty-four grams (0.77 mole) of ethyl bromide, nineteen grams (0.80 mole) magnesium turnings, and forty-nine grams (0.39 mole) of 2-acetyl thiophene.

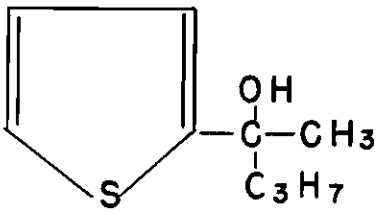
The procedure was exactly the same except that the temperature during the entire reaction was kept at 0 to 5 degrees C. The reaction mixture was hydrolyzed in the usual manner and extracted with 500 ml. of ether. This extract was dried over anhydrous potassium carbonate and the ether distilled off at 50 degrees C.

The residue was distilled under reduced pressure and the pure product boiled at 107 degrees C. at 20 mm. The yield was thirty-two grams or 54% of theoretical.

The product was a colorless oil with a refractive index of 1.5288 at 20 degrees C. The density at 20 degrees C. was 1.081. The molecular refraction was found experimentally to be 44.40, the theoretical value being 45.45.

Analysis for carbon and hydrogen gave values of 60.8% and 7.61%, respectively, as compared with a calculated value of 61.5% carbon and 7.70% hydrogen.

Preparation of Methyl n-Propyl 2-Thienyl Carbinol III



Eighty-one grams (0.66 mole) of propyl bromide in 120 ml. anhydrous ether was slowly dropped in a dry 500 ml. three-necked flask equipped with a condenser with drying tube, dropping funnel, and mechanical stirrer. The flask contained sixteen grams (0.66 mole) of magnesium turnings and the addition took thirty-five minutes. Cooling was necessary and the solution was stirred fifteen minutes after the addition was complete.

The Grignard solution was cooled to 0-5 degrees C. and forty grams (0.325 mole) of 2-acetyl thiophene was dropped in over thirty minutes. The solution was stirred one hour after this addition.

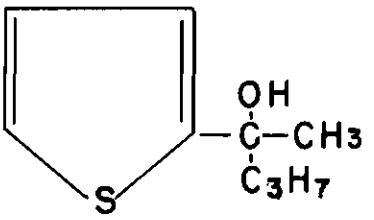
The Grignard complex was hydrolyzed in the usual manner and the ether extract dried overnight with potassium carbonate.

The ether was distilled off at 50 degrees C. and the residue fractionated at reduced pressure. The pure product boiled at 102 degrees C. at 8 mm. The yield was 31.5 grams or 57.7% of the theoretical.

The carbinol was a colorless oil with a rather pleasant odor. The refractive index at 20 degrees C. was 1.5220 and the density at the same temperature was 1.050.

The molecular refraction was found experimentally to be 49.40 compared with an actual value of 50.18. Carbon and hydrogen analysis gave 63.8% carbon and 8.38% hydrogen. The theoretical values are 63.6% carbon and 8.25% hydrogen.

Preparation of Methyl Isopropyl 2-Thienyl Carbinol IV



Methyl isopropyl 2-thienyl carbinol was prepared using the same general procedure as in the previous experiment.

Seventeen grams (0.71 mole) of magnesium turnings were placed in the flask and eight-seven grams (0.71 mole) of isopropyl bromide in 120 ml. anhydrous ether dropped in slowly over a period of one hour. Cooling was necessary as the reaction became rather violent. The solution was stirred five minutes after the addition of all the isopropyl bromide.

The Grignard solution was cooled and forty-five grams (0.35 mole) of 2-acetyl thiophene dissolved in 50 ml. anhydrous ether was dropped in over a period of twenty minutes with cooling. A heavy precipitate formed in the flask as in the previous experiments and the complex was stirred one hour after the addition was complete.

Hydrolysis was effected in exactly the same manner as in the preparation of methyl propyl 2-thienyl carbinol. The solution was extracted and dried over anhydrous potassium carbonate. The ether was evaporated and the residue fractionated.

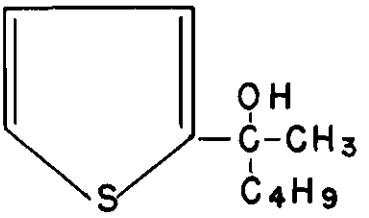
The pure methyl isopropyl 2-thienyl carbinol was a colorless to slightly yellow oil boiling at 91.5 degrees C. at 8 mm. The yield

was 31.5 grams or 53.0% of the theoretical.

The refractive index at 20 degrees C. was 1.5268 and the density at this temperature was 1.068. The molecular refraction found experimentally was 48.90 and the theoretical value is 50.18.

The per cent carbon and hydrogen found by analysis was 62.0% carbon and 8.19% hydrogen as compared with a theoretical value of 63.6% carbon and 8.25% hydrogen.

Preparation of Methyl Butyl 2-Thienyl Carbinol V



Ninety grams (0.66 mole) of n-butyl bromide dissolved in 115 ml. of anhydrous ether was dropped into the 500 ml. flask containing sixteen grams (0.66 mole) of magnesium turnings. The same procedure was used as in the preceding experiment. The addition of the n-butyl bromide took forty-five minutes. In this case, the reaction did not start immediately, and it was necessary to start a small Grignard reaction in a test tube and add this to the contents of the flask. Upon addition of this catalyst the reaction proceded in the normal way.

After addition of the n-butyl bromide the mixture was stirred fifteen minutes and cooled to 0-5 degrees C. Forty-one grams (0.33 mole) of 2-acetyl thiophene dissolved in 50 ml. absolute ether was dropped in over a period of thirty minutes. No precipitate formed in this case. The solution was stirred one hour after the addition and hydrolyzed as before.

The hydrolyzed solution was extracted, filtered, and dried over anhydrous potassium carbonate. The ether was distilled off at 40-60 degrees C. and the residue fractionated.

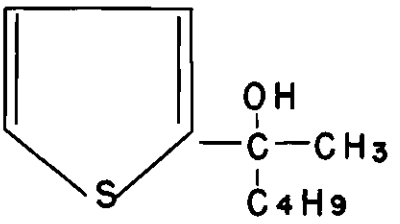
The pure methyl butyl 2-thienyl carbinol boiled at 107 degrees

C. at 7 mm. The yield was thirty-nine grams or 65% of theoretical.

The product was a colorless, viscous, oil with a sweet but somewhat irritating odor. The refractive index and density at 20 degrees were 1.5165 and 1.028, respectively.

The experimental molecular refraction was 54.10 as compared with a calculated value of 54.78. Carbon and hydrogen analysis gave 64.8% carbon and 8.62% hydrogen. The theoretical values are 65.3% carbon and 8.7% hydrogen.

Preparation of Methyl sec-Butyl 2-Thienyl Carbinol VI



The same set-up was used in this experiment as in the preparation of methyl n-butyl 2-thienyl carbinol. Forty-five grams (0.33 mole) of sec-butyl bromide was dissolved in 50 ml. anhydrous ether and dropped slowly into the flask containing seven and eight tenths grams (0.33 mole) of magnesium turnings and 25 ml. anhydrous ether. It was found that adding the halide to the magnesium turnings in ether gave a smoother reaction than adding it to the dry magnesium. The addition took twenty-five minutes.

The solution was cooled to 0-5 degrees C. and twenty grams (0.16 mole) of 2-acetyl thiophene in 25 ml. anhydrous ether was added over forty minutes. This solution was stirred one hour and hydrolyzed.

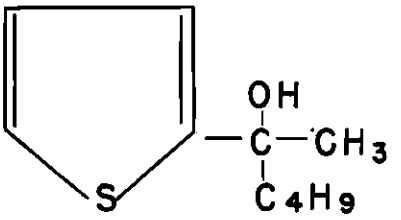
After extracting and drying with anhydrous potassium carbonate, the ether was distilled off and the residue fractionated under reduced pressure.

The pure methyl sec-butyl thienyl carbinol boiled at 107 degrees C. at 10 mm. pressure. It was a colorless oil with an odor similar to those carbinols previously prepared. The yield was 10.8 grams or 36.0% of the theoretical.

The refractive index and density at 20 degrees were 1.5314 and 1.078, respectively. The molecular refraction determined experimentally was 52.50 and the theoretical value was 54.78.

Analysis for carbon and hydrogen gave 66.1% carbon and 8.85% hydrogen as compared with theoretical values of 65.3% carbon and 8.70% hydrogen.

Preparation of Methyl ter-Butyl 2-Thienyl Carbinol VII



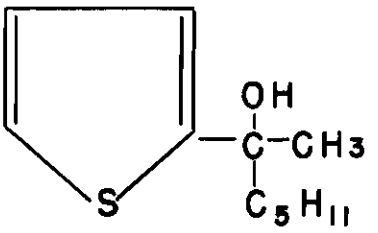
Methyl ter-butyl 2-thienyl carbinol (VII) was prepared by the interaction of 2-acetyl thiophene and ter-butyl magnesium bromide in exact accordance with the procedure used in the preparation of sec-butyl 2-thienyl carbinol. The carbinol was obtained in a 33% yield (20 grams).

The pure product was a colorless oil possessing a pungent odor which boiled at 102 degrees C. at 14 mm. pressure.

The refractive index and density at 20 degrees were 1.5450 and 1.109, respectively. The molecular refraction found experimentally was 52.60, the theoretical being 54.78.

Carbon-hydrogen analysis gave 65.8% carbon and 8.50% hydrogen as compared with theoretical values of 65.3% carbon and 8.7% hydrogen.

Preparation of Methyl n-Amyl 2-Thienyl Carbinol VIII



The same general procedure was used in this preparation as in all previous experiments. The Grignard reagent was prepared by the action of 92 grams (0.60 mole) n-amyl bromide on fourteen grams (0.60 mole) magnesium turnings. It was necessary to start the reaction by the addition of a small amount of the Grignard reagent prepared in a test tube. The temperature of the bath was maintained at 0 degrees C.

To the n-amyl magnesium bromide at 0 degrees was added 38 grams (0.30 mole) of 2-acetyl thiophene over a period of thirty minutes and the complex formed was stirred thirty minutes.

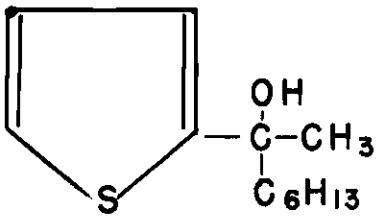
After hydrolysis, extraction, and drying, the ether was distilled off and the residue subjected to vacuum distillation.

The pure methyl n-amyl 2-thienyl carbinol (VIII) was a colorless oil obtained in a yield of 61.5% of the theoretical (37 grams). The boiling point was 118 degrees C. at 5 mm.

The refractive index at 20 degrees was 1.5100 and the density at this temperature was 1.020. The experimental molecular refraction was 58.10 and the theoretical value was 59.28.

Carbon-hydrogen analysis gave 66.2% carbon and 8.91% hydrogen. The theoretical values are 66.7% carbon and 9.08% hydrogen.

Preparation of Methyl n-Hexyl 2-Thienyl Carbinol IX



Methyl n-hexyl 2-thienyl carbinol (IX) was prepared by the exact procedure outlined for methyl n-amyl 2-thienyl carbinol, the same molar quantities being used. The temperature was maintained at 0-5 degrees C. for the entire reaction.

The pure product was obtained in a yield of 65% (38.9 grams) and boiled at 123 degrees C. at 5 mm. pressure.

The refractive index and density were 1.5068 and 1.002, respectively, both taken at 20 degrees C. The experimental molecular refraction was 63.00 and the theoretical value was 64.00.

The per cent carbon and hydrogen found were 67.6% carbon and 9.22% hydrogen as compared with theoretical values of 68.0% and 9.44%.

CHAPTER IV

GENERAL DISCUSSION OF RESULTS

GENERAL DISCUSSION OF RESULTS

The preparation of a number of thienyl substituted tertiary alcohols through the Grignard synthesis was accomplished. This extended the work of Thomas[3] who prepared the first member of the series, dimethyl 2-thienyl carbinol (1). The greatest competing reaction in the synthesis was the dehydration of the alcohols during preparation or purification. The conditions, therefore, were kept as mild as possible in all reactions to prevent loss of water and formation of olefins.

Yields varied from 33% to 65%, the best yields being obtained when using alkyl bromides rather than iodides. This seems to be general in Grignard reactions since the presence of an iodide might presumably catalyze dehydration. The secondary and tertiary magnesium halides in general gave lower yields than the normal isomers. This is probably due to steric factors.

In determining the physical constants of the alcohols, the same apparatus and methods were used throughout. All constants for a given carbinol were determined on the same sample. The densities were determined at 20° with a bottle type pycnometer. Refractive indices were determined with an Abbe refractometer with its prism controlled by water from a constant temperature bath. The boiling points were determined at reduced pressures with a Cottrell type boiling point apparatus. Carbon and hydrogen determinations were made with the customary combus-

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[3] Ibid.

tion apparatus with a trap of PbO_2-Pb_3O_4 in the tube to remove sulfur dioxide formed.

The alcohols when first prepared were colorless, however, if allowed to stand at room temperature for any appreciable length of time, they became slightly yellow. This is to be attributed to their easy dehydration and polymerization. Because of this decomposition, they were stored under refrigeration.

With the exception of the first member of the series, dimethyl 2-thienyl carbinol (I), all the carbinols were oily liquids, the lower members having a sweet odor which became pungent as the molecular weight increased.

In general the refractive indices decreased in a fairly regular rate with increase in molecular weight for the compounds in which the side chain was not branched. This decrease is also observed in the analogous compounds containing a phenyl group in place of the thienyl ring.[4,5] When the side chain was branched there were deviations in the regularity which is not uncommon.

The densities also decreased in a regular way in the non-branched compounds. Deviations in this regularity were again noted for the carbinols substituted with a branched side-chain.

In all cases a depression was shown in the molecular refraction of these compounds. This seems to be general with thiophene derivatives

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[4]A. Klages, Ber., 35, 3507 (1902).

[5]Ibid., p. 2643.

possessing a saturated side-chain.[6,7] The values for the atomic refractions of carbon, hydrogen, and oxygen were taken from standard tables.[8] The value for the atomic refraction of sulfur was that determined by Price and Twiss.[9]

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[6]M. A. Youtz and P. P. Perkins, J. Am. Chem. Soc., 51, 3511 (1929).

[7]F. S. Fawcett and H. E. Rasmussen, J. Am. Chem. Soc., 67, 1705 (1945).

[8]Landolt-Bornstein, Physikalisch-Chemische Tabellen, Vol. 5, p. 985.

[9]T. S. Price and D. F. Twiss, J. Chem. Soc., 101, 1263 (1912).

CHAPTER V

SUMMARY

SUMMARY

The following compounds have been prepared, and a study made of some of their properties.

Carbinols

Dimethyl 2-thienyl (I)

Methyl ethyl 2-thienyl (II)

Methyl n-propyl 2-thienyl (III)

Methyl isopropyl 2-thienyl (IV)

Methyl n-butyl 2-thienyl (V)

Methyl sec-butyl 2-thienyl (VI)

Methyl ter-butyl 2-thienyl (VII)

Methyl n-amyl 2-thienyl (VIII)

Methyl n-hexyl 2-thienyl (IX)

APPENDIX I

TABLE I

PHYSICAL PROPERTIES

Carbinol	Yield %	B.p. °C.	Press. mm	Density 20°	Ref. Index 20°
Dimethyl 2-thienyl	33.2	104-5	25		
Methyl ethyl 2-thienyl	54.0	107	20	1.081	1.5288
Methyl n-propyl 2-thienyl	57.7	102	8	1.050	1.5220
Methyl iso-propyl 2-thienyl	52.6	91.5	8	1.068	1.5268
Methyl n-butyl 2-thienyl	65.0	107	7	1.028	1.5165
Methyl sec-butyl 2-thienyl	36.0	107	10	1.078	1.5314
Methyl ter-butyl 2-thienyl	33.0	102	14	1.109	1.5450
Methyl n-amyl 2-thienyl	61.5	118	5	1.020	1.5100
Methyl n-hexyl 2-thienyl	65.0	123	5	1.002	1.5068

APPENDIX II

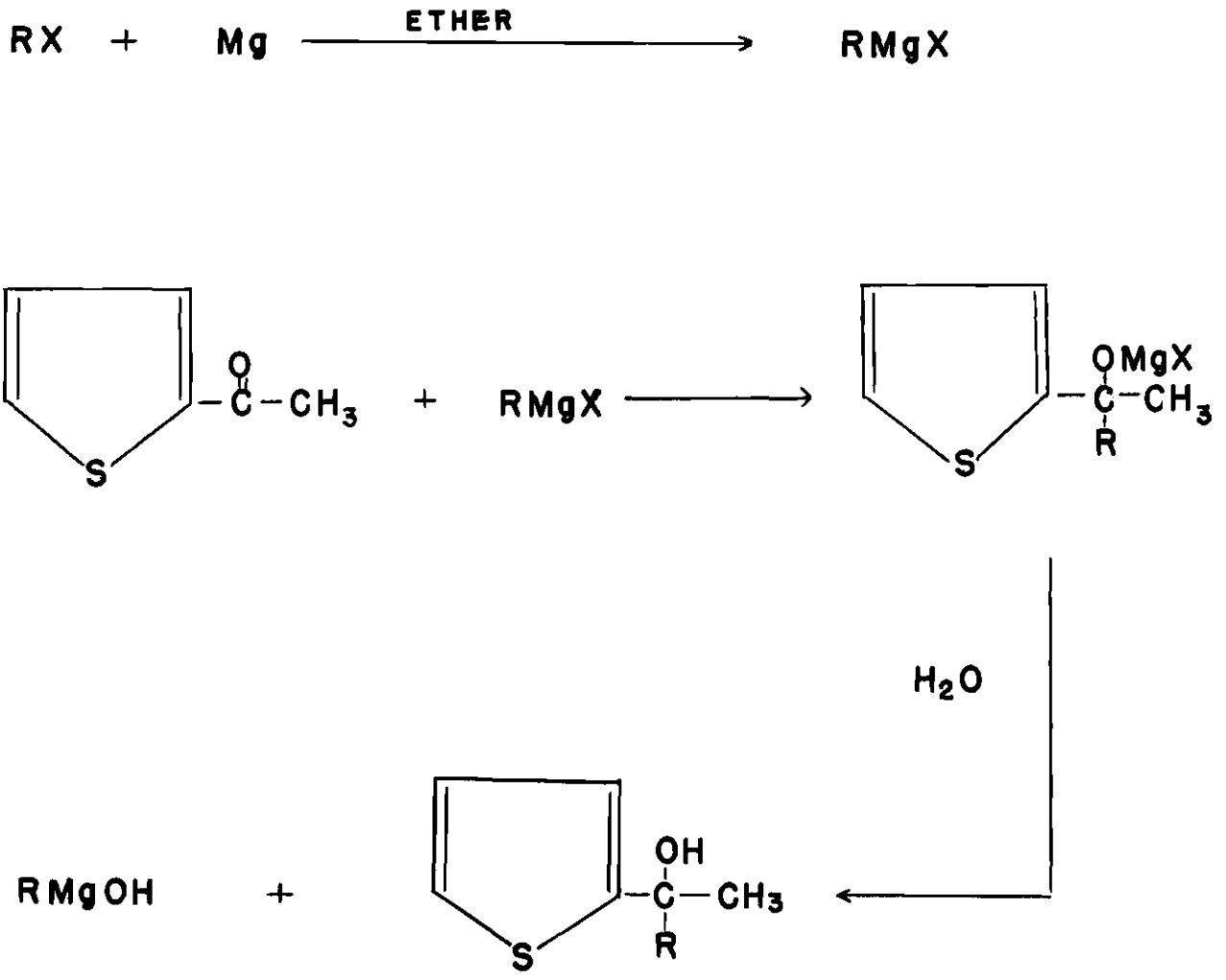
TABLE II

ANALYSIS

Carbinol	Molecular Refraction Found	Calc.	Carbon Cal.	Found	Hydrogen Cal.	Found
Methyl ethyl 2-thienyl	44.40	45.45	61.5	60.8	7.70	7.61
Methyl n-propyl 2-thienyl	49.40	50.18	63.6	63.8	8.25	8.38
Methyl iso-propyl 2-thienyl	48.90	50.18	63.6	62.0	8.25	8.19
Methyl n-butyl 2-thienyl	54.10	54.78	65.3	64.8	8.70	8.62
Methyl sec-butyl 2-thienyl	52.50	54.78	65.3	66.1	8.70	8.85
Methyl ter-butyl 2-thienyl	52.60	54.78	65.3	65.8	8.70	8.50
Methyl n-amyl 2-thienyl	58.10	59.28	66.7	66.2	9.08	8.91
Methyl n-hexyl 2-thienyl	63.00	64.00	68.0	67.6	9.44	9.22

FIGURE 1

REACTION OF ALKYL MAGNESIUM HALIDES WITH 2-ACETYL THIOPHENE



APPENDIX III

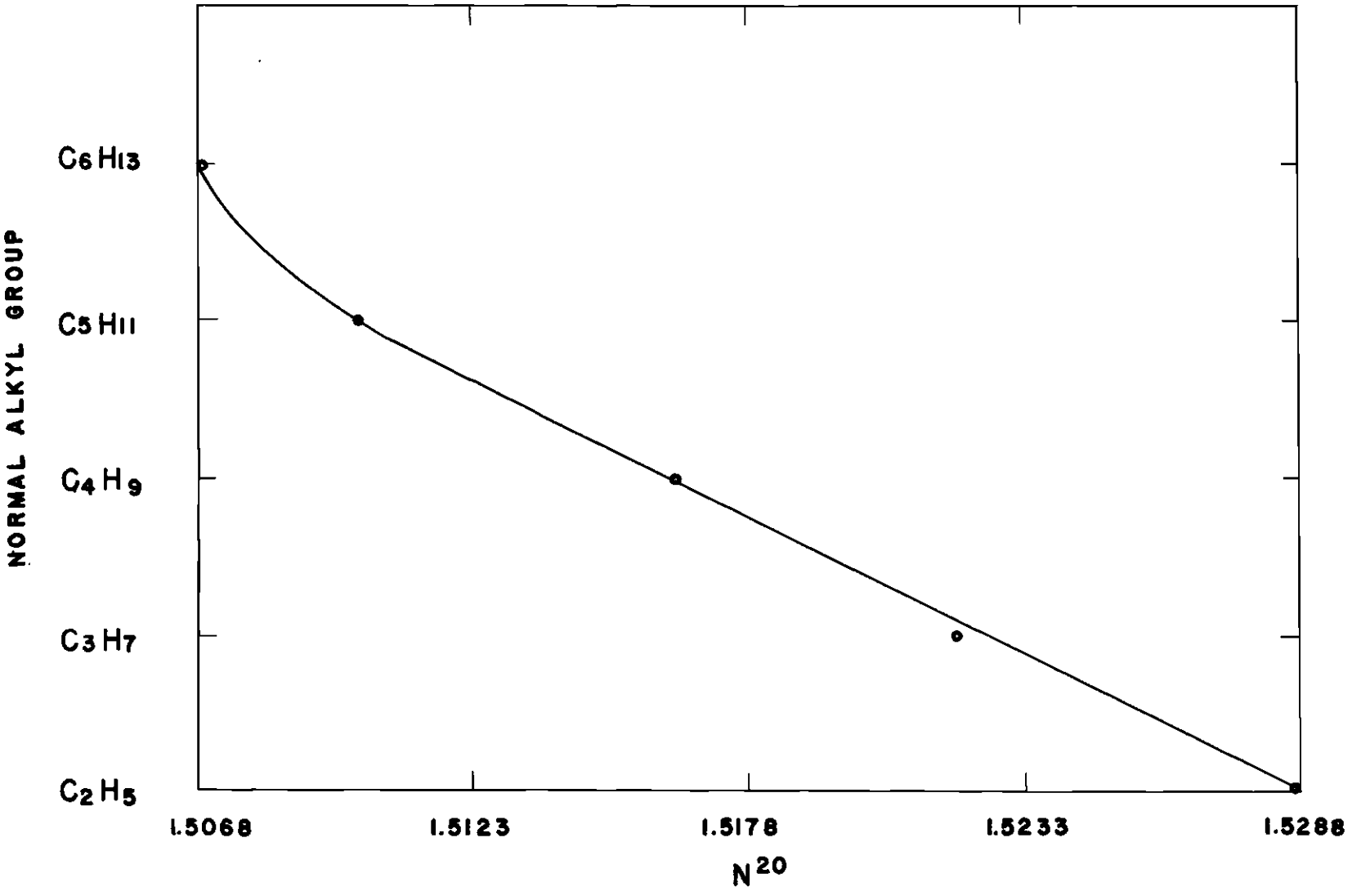


FIGURE 11

REFRACTIVE INDEX vs SIDE CHAIN

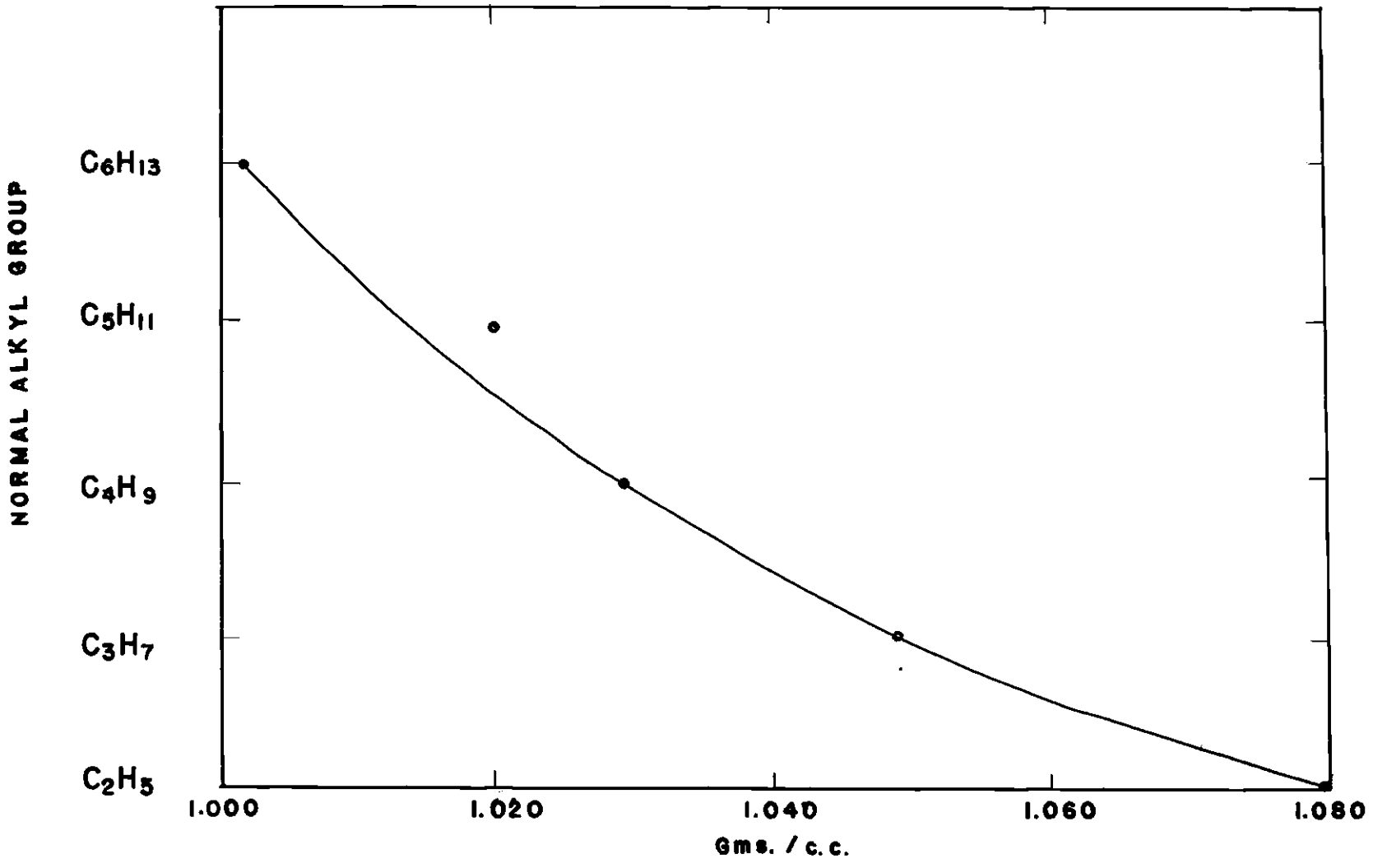


FIGURE 1

DENSITY vs SIDE CHAIN

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